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Synthetic Studies on Anticancer Compounds: The Tylophorinines

Conrad Gracjan Kaczmarek
University of Tennessee - Knoxville

To the Graduate Council:

I am submitting herewith a thesis written by Conrad Gracjan Kaczmarek entitled "Synthetic Studies on Anticancer Compounds: The Tylophorinines." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

David C. Baker, Major Professor

We have read this thesis and recommend its acceptance:

John F. Turner, Gary Sayler

Accepted for the Council:
Dixie L. Thompson

Vice Provost and Dean of the Graduate School

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Synthetic Studies on Anticancer Compounds: The Tylophorinines

A Thesis
Presented for the
Master of Science
Degree
The University of Tennessee, Knoxville

Conrad Gracjan Kaczmarek
May 2004

Dedication

To My Family

Acknowledgments

I would like to thank Dr. D. C. Baker for his support, input, and use of laboratory, without which this project would not be possible. From among the members of the Baker research group, I would like to thank Ambroise Akue, for help with the general necessities while in the course of or preparation for many experiments; Julio Guitierrez, for helping in the synthesis of many of these compounds; Riyam Kafri, for acquiring many of the HPLCs to provide proof of purity; Dr. M. Li, for helping in the synthesis of many compounds as well as his input into the synthetic strategy for the project; Dr. K. T. Welch, for helping with the acquisition and interpretation of some of the NMR data; and Dr. S. Zhong, who began this project and developed much of the chemistry for these types of compounds. I would also like to thank the following from the Department of Chemistry at the University of Tennessee: Dr. H. Pan, for helping with the acquisition of NMR data; Dr. F. M. Schell, for conversations related to alkaloid chemistry; Dr. A. Tuinman, for acquiring mass spectrums, interpreting them, and discussing possibilities when problems arose; and Dr. J. F. C. Turner, for conversations regarding the synthetic strategy. Finally, I would like to thank my family for their encouragement, support, and patience.

Abstract

This thesis describes synthetic studies in the area of alkaloid chemistry, specifically, potent anticancer compounds: the tylophorinines.

Tylophorinine is a naturally occurring compound found in the Monarch butterfly and plants of the genus *Tylophora*. Described here is a concise methodology for stereoselective synthesis of this compound, and analogs, starting from simple, naturally occurring compounds. The synthetic strategy represents a simplification in synthesizing tylophorinines, and would allow numerous other tylophorinines with similar chemical structure to be conveniently synthesized in an analogous fashion.

Further, the tylophorinines are convenient compounds for determining where a cancer cell may be most effectively attacked. Numerous attempts were made to alkylate and then biotinylate a tylophorinine, in the hopes that a cancer protein would be snared, leading to the determination of the tylophorinines mode of action in the cancer cell.

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List of Schemes

Abbreviations

AcOH	Acetic acid
Ac_2O	Acetic anhydride
BMPAC	1,3-bis-methoxycarbonylpropylammonium chloride
DCC	1,3-dicyclohexylcarbodiimide
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
LAH	Lithium aluminum hydride
L-Sel	L-selectride
MeOH	Methanol
NHS	*N*-hydroxysuccinimide
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran

I. Introduction

1. Background on cancer

As society progresses, so does its technology and the ability to eliminate or resist various diseases. Among the many accomplishments in various fields over the years, a few have stood as prime examples: Watson and Crick's elucidation for the structure of DNA, Salk's polio vaccine, and Woodward's synthesis of strychnine. These incredible accomplishments have inspired others to pursue feats in their fields for the betterment of society. However, one disease has eluded many brilliant minds of our time from discovering a cure: cancer.

Unlike most diseases, cancer is a genetic alteration of the cell, which reproduces autonomously and eventually overwhelms and kills the "host".[1] Its causes, although widely speculated and argued,[1-3] remain an essential "black box." Hence the most elusive question is: how and why does a cell transform itself into something incompatible with the "functional" living system? As stated, there are many hypothetical answers that serve for good theory, but no definitive proof has yet presented itself. Other questions are: how does one destroy a natural mutation without hurting healthy cells in the process? And what makes a cancer cell different enough from a healthy cell so that a drug may selectively act upon the mutant?

Of course, there are numerous striking differences between cancer and healthy cells,[1-4] the most pronounced of which is the genetic alterations that result leading to two primary differences that are apparent across various cell lines. One is that cancer can use the glycolytic pathway, in place of oxygen, almost exclusively in order to survive.[3,4] So,

much like a fungus, it "eats up" the body's natural reserves of sugars producing an acidic environment.[3,4] Typically, normal tissue has a blood pH of 7.4, whereas in cancers have pH ranges of 6.5–6.8, with some as low as 5.5.[4] Second, cancer cells tend to have higher rates of proliferation with respect to normal cells.[1-4] Surgery and radiotherapy have been relatively unsuccessful in effectively curbing growth while maintaining a reasonable standard of living for the patient. However, pharmaceuticals entering the body to a great extent have not been able to make a significant distinction between cancer and normal cells.[3] Taxol, has been perhaps the brightest accomplishment in the fight against cancer. However, its use has been primarily employed in ovarian cancer,[5] and although its core skeleton may be viewed as a pharmacophore for other types of anti-cancer agents, little significant progress has been made since taxol has been introduced into clinical usage. But the acidic environment provides an advantage in that alkaloids, being basic, can survive by forming salts in cancer cells until the appropriate "receptor" is found whereby the alkaloid may interact with and "kill" the cancer cell.

2. *Tylophora* alkaloids in cancer

A few years ago, an Indian group made a suprising discovery.[6] They had isolated a new series of compounds from plants of the genus *Tylophora*, the tyloindicine compounds, some of which are the most potent antitumor compounds discovered to date.[7] Tyloindicine's molecular skeleton is represented in Figure 1. Chemically, tyloindicines are represented with an indolizidine ring system fused to a saturated phenanthrene with the exocyclic double bond. The aromatic rings may contain various substitution patterns. Initially, the compound in Figure 1 was the one most sought after. The aromatic system

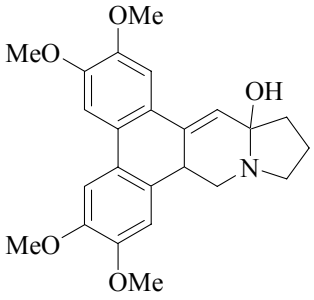
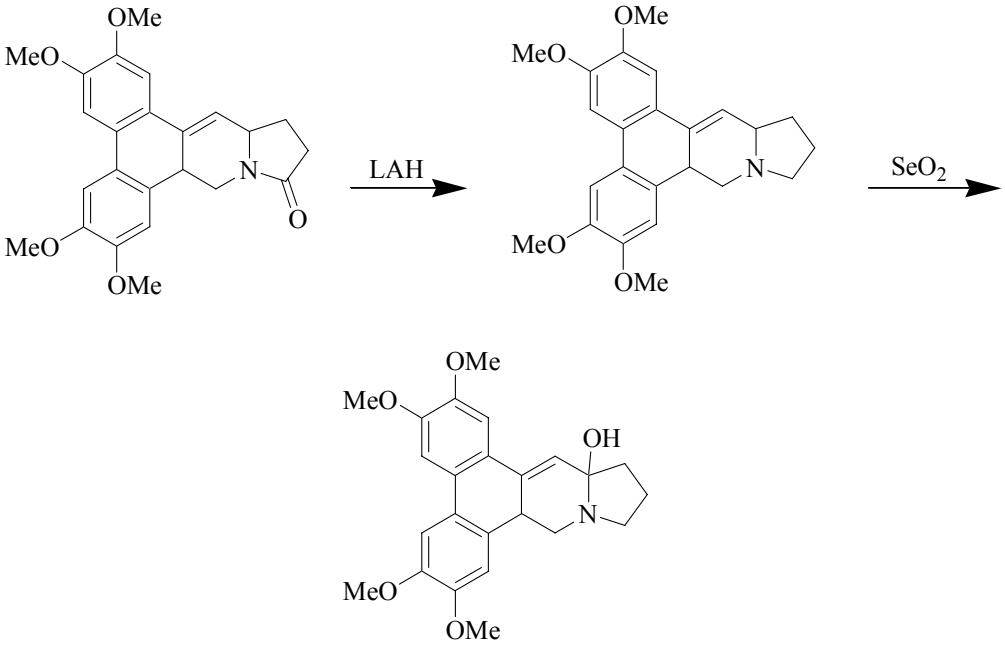


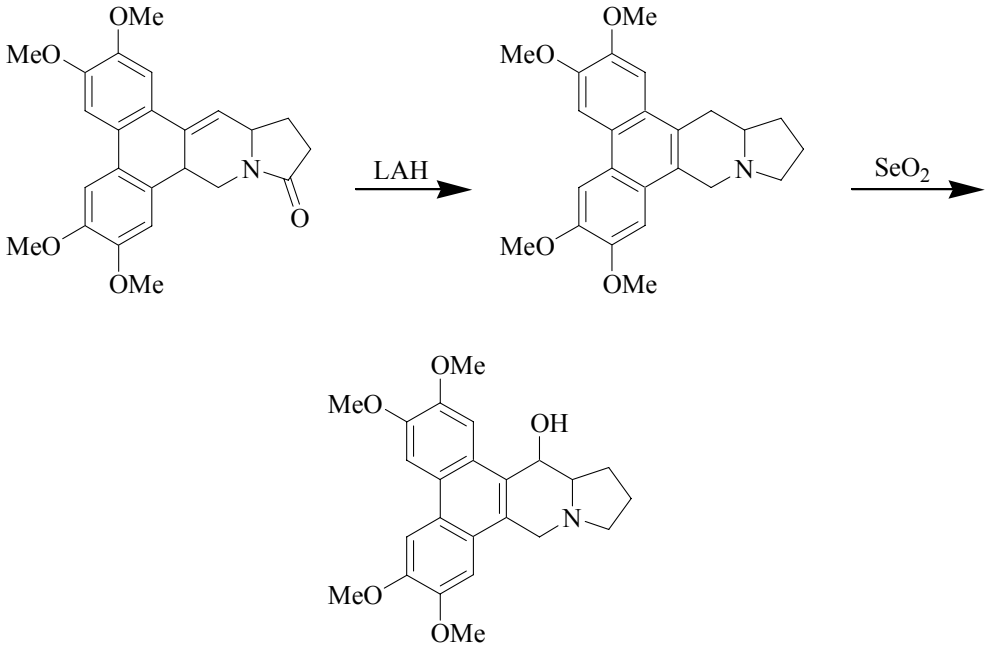
Figure 1. Tyloindicine G

contains four methoxy groups, but the interesting functionality is the allylic hemi–aminal. To date there is no procedure to effectively form this functionality. Thus the need to discover efficient synthetic routes to these compounds became imperative in order to produce sufficient quantities to effectively study their properties towards cancer. Scheme 1 shows the initial attempt at formation of the allylic hemi-aminal. However, it was later proven that double-bond rearrangement occurs leading to phenanthrene ring formation and a benzylic alcohol, as shown in Scheme 2. Fortunately, it was discovered that the tylophorinine produced is also a very active agent against cancer. In pharmacological studies, it has been shown that compound **1** (Figure 2), with the S configuration at the hydroxy position, is very active as an anti-cancer agent.[7]

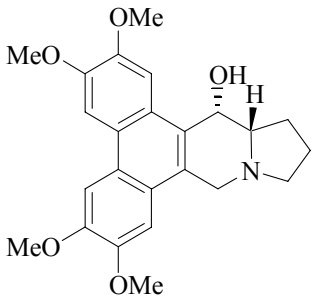
The tylophorinines differ from the tyloindicines in two respects: 1. the position of the double bond forming the fully aromatic phenanthrene system, and 2. an alcohol *alpha* to the phenanthrene ring. However, the question remains, how exactly do these compounds behave in the cancer cell?



Scheme 1. Attempted synthesis of Tyloindicine G



Scheme 2. Resultant products from attempted synthesis of Tylo G



1

Figure 2. S-hydroxytylophorinine

3. Biotinylation for determination of mode of action

The previous question was determined to be answered by creating a molecule which is known to be active against cancer cells with a "side group" attached that is easily detectable by modern methods. First, given the anti-cancer activities shown by variously substituted tylophorine-type alkaloids,[8-15] i.e., that substitution on the phenanthrene part can be varied and activity preserved, one can assume that the activity primarily resides in the indolizidine part of the molecule. Hence, it was decided that the detection system should be furthest away from this region. Thus, second, a link between the active molecule and detection system was necessary. This part of the molecule was determined to consist of a six-membered aliphatic chain as the most effective bridge.[16] Third, employment of the biotin–avidin complex was determined to best suit the detection system because it is very strong and easily quantifiable[17-19]. The biotin–avidin complex is often used for cytochemical localization and isolation of receptor studies. Finally, an

amide bond between the linker chain and the biotin was determined to be the proper functionality due to its strength and resistance to many chemical environments. Thus, the structure of the target compound is represented by Figure **3**.

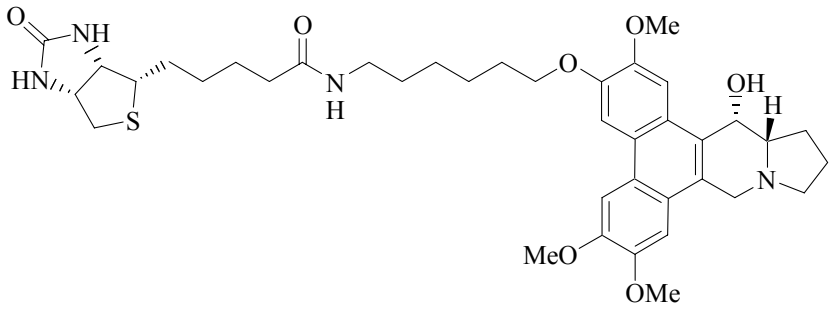


Figure 3. Biotinylated tylophorinine

II. Statement of Problem

1. Methodology for tylophorinine synthesis

It was found that the active tylophorinine was first synthesized by Rapoport.[20] However, the procedure leading to the compound lacked necessary details for efficient production. Hence, it was determined that we needed to develop a similar synthetic route that would facilitate production for the desired tylophorinine, as well as tylophorinines with varying aromatic substitution patterns.

2. Biotinylation of tylophorinine

To produce the biotinylated tylophorinine, Figure **3**, the modified Rapoport procedure was employed. In the course of study, several problems arose that required further modification, for example, the oxidative coupling strategy. More importantly, a linker arm was required that would alkylate the phenolic hydroxy group at an appropriate position in the synthesis while maintaining the overall synthetic design. It was determined that the alkylation of the alkaloid should occur following cyclization of the basic molecular skeleton. This was done in order to avoid numerous difficult protection and deprotection strategies. The procedure would then be followed to completion forming the desired tylophorinine with one step remaining to link with biotin.

III. Results and Discussion

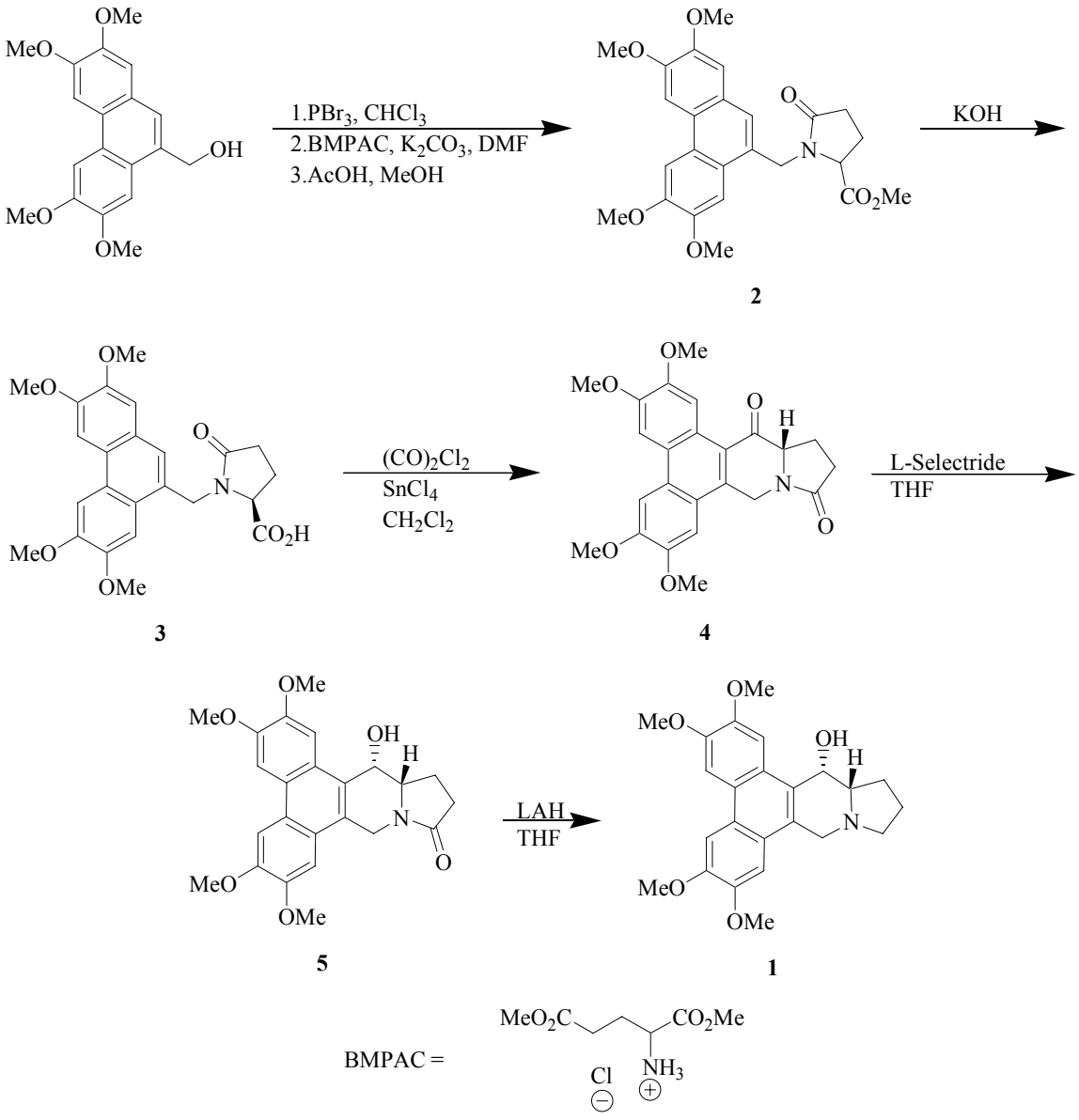
1. Preparation of *S*-hydroxytylophorinine

Repeating Rapoport's synthesis[20] was a primary concern, since the effectiveness of the procedure had to be proven. It was found in the course of preparation that simplifications could be made (Scheme 3). For example, the preparation of **2** proved to essentially be a one-pot reaction with only minor separations necessary. It was found that the amine was not separable from the amide, but the amide could be purified since self-condensation is essentially irreversible. Ester hydrolysis to **3**, followed by cyclization to **4**, provides the core indolizidine ring skeleton of the tylophorinine. Stereoselective reduction of the ketone employing L-Selectride yields compound **5**. The Rapoport paper[20] extensively explains the identification between the α and β isomers. Finally, reduction of the amide gives the biologically active compound **1**. In repeating this procedure, reproducible spectra were obtained which further validated the use of this procedure. With this information it became possible to develop a strategy towards the synthesis of the biotin-linked compound in Figure 3.

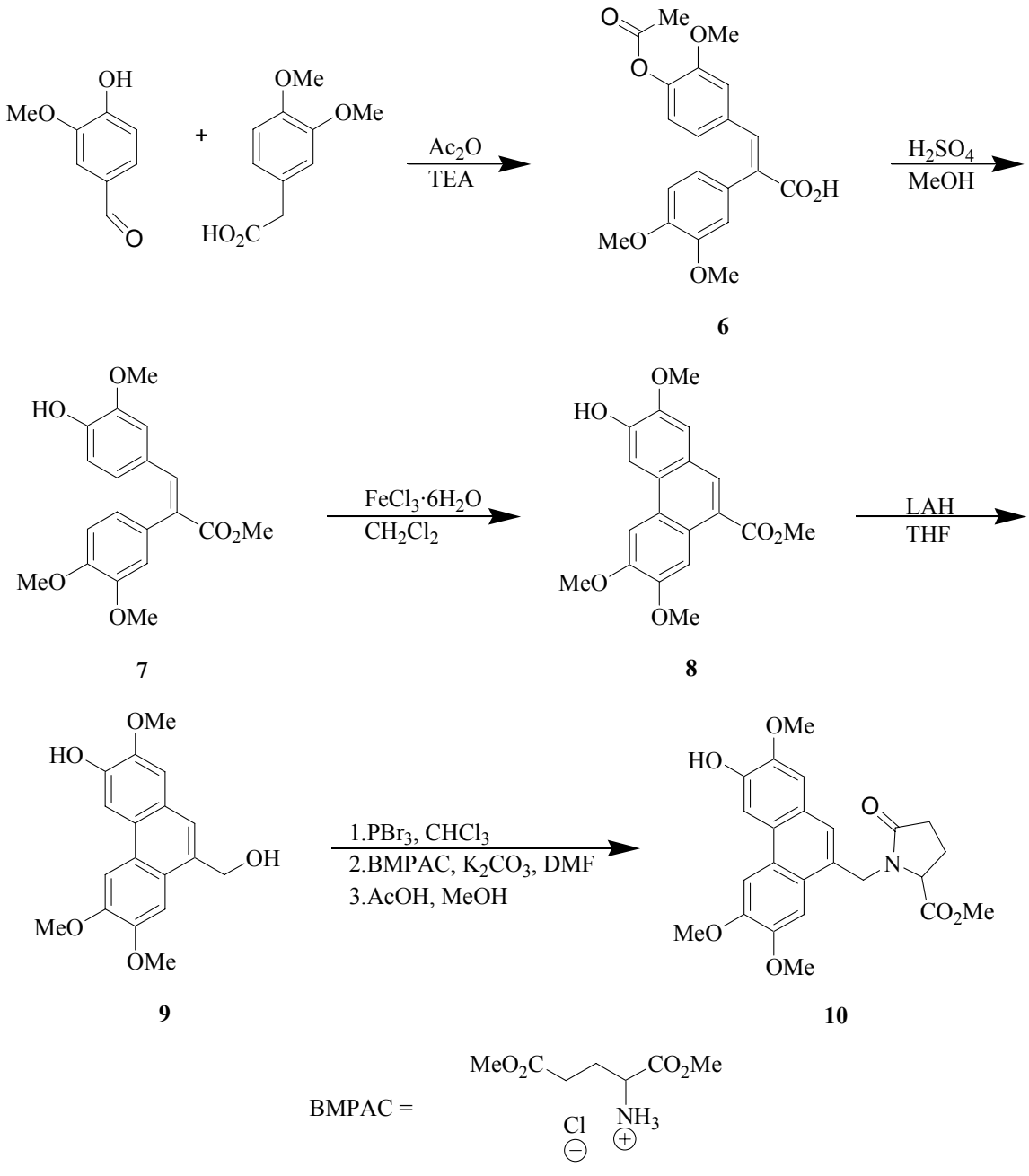
2. Synthetic studies toward tylophorinine biotinylation

a. Synthesis of free hydroxy tylophorinine

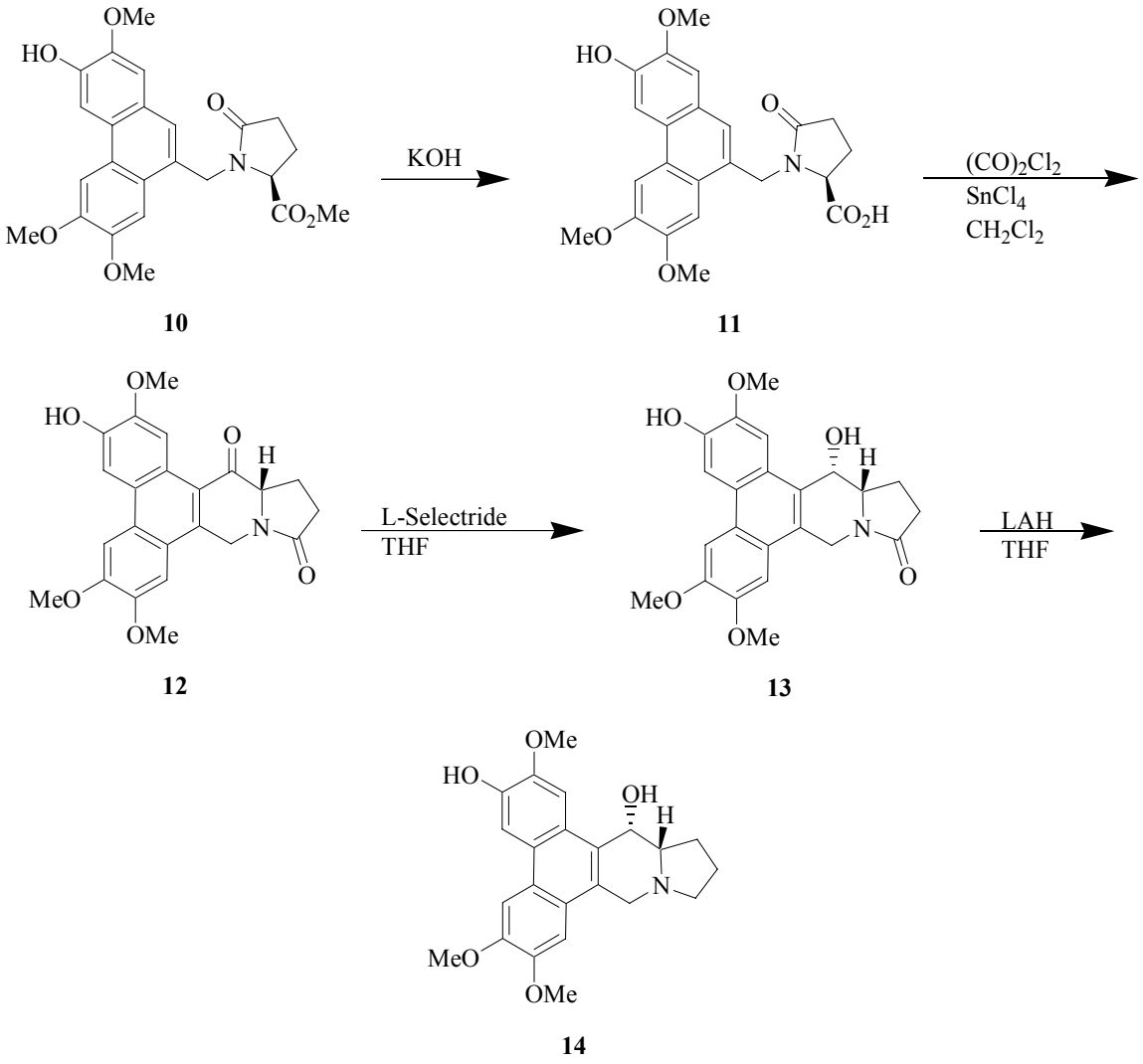
The synthesis as depicted in Scheme 4 opens with a condensation to form a *cis*–stilbene system, **6**. 3-(4-Acetoxy-3-methoxyphenyl)-2-(3,4-dimethoxyphenyl)acrylic acid.[21] Fieser mentions that the reaction's cis/trans ratio for this type of reaction is approximately 10 to 1.[22] However, the condensation was performed without methoxy-substituted aromatic rings. In the process the phenolic hydroxy group is acetylated,



Scheme 3. Preparation of S-hydroxytylophorine



Scheme 4. Synthesis tylophorinine for biotinylation



Scheme 4 (contd.)

which helps to avoid future problems associated with this synthesis. The NMR spectrum of the purified compound showed no additional signals to indicate that any significant amount of the trans compound was produced. Alternatively, it is conceivable that the trans compound does not recrystallize. Second and third crops from the mother liquor that were recrystallized also produced identical results. In either case, the intended goal of synthesizing pure cis compound is effectively accomplished.

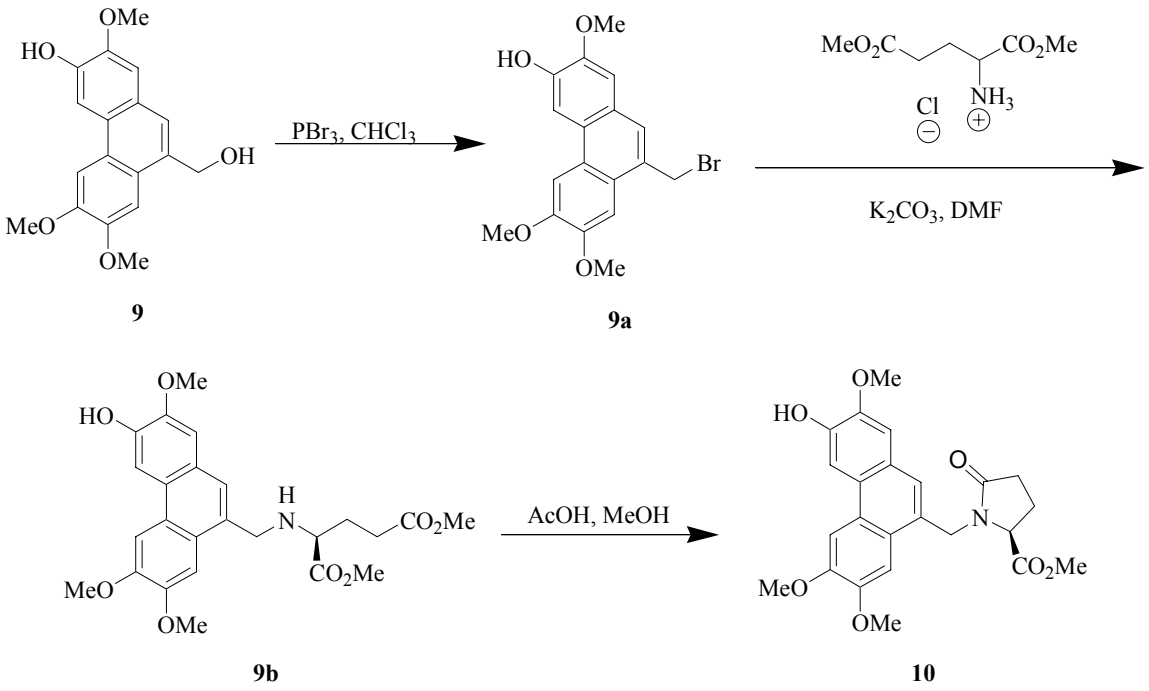
Formation of the 2-(3,4-dimethoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)acrylic acid methyl ester (**7**) by standard Fischer esterification procedure proceeds in high yield.[21] Ester formation is necessary for the preparation of the phenanthrene ring since carboxylic acids and some types of free alcohols tend to react with reagents that promote the reaction. A methyl ester was chosen because it is easily reducible to the corresponding alcohol. The acetyl group is also lost in the process. This forms the phenolic hydroxy group which is necessary for iron(III) chloride to react effectively. This provides an inexpensive method to phenanthrene ring formation.

The phenanthrene ring system is a central component of the tylophorinines. Its formation early in the synthesis is important because it allows manipulation to form the indolizidine ring system without potential decomposition and side reactions associated with the stilbene ring system. The phenolic hydroxy group presents problems here, however. Typically in modern syntheses VOF_3 is the preferred reagent for bridging the phenyl rings.[23-26] Hydroxy groups interfere with the action of VOF_3 probably by reacting with the vanadium (use of VOF_3 in this synthesis is discussed further in section III.2.b) itself in a manner that completely destroys the reagent. This problem is overcome with

the use of $FeCl_3 \cdot 6H_2O$.[27,28] The iron(III) chloride specifically reacts with phenolichydroxy groups in phenolic couplings. This bondng activates the aromatic system with electron donation from the iron, thus producing, 3-hydroxy-2,6,7-trimethylphenanthrene-9-carboxylic acid methyl ester (**8**). At the expense of time, the advantage to this reaction is its low cost.

Reduction of compound **8** to 9-hydroxymethyl-2,6,7-trimethoxyphenanthren-3-ol (**9**) is performed with $LiAlH_4$.[29] The reaction proceeds smoothly with no side-product formation.

The next series of reactions in Scheme 4, intermediates depicted in Scheme 5, introduces the nitrogen to form, 1-(3-hydroxy-2,6,7-trimethoxy-phenanthren-9-ylmethyl)-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (**10**), at the primary alcohol position. It commences with bromide formation by alcohol displacement on to give **9a**.[30] This displacement proceeds smoothly and in high yield. The only drawback is that the excess phosphorus must be removed for introduction of the amino acid. Since the separation is between water and chloroform, some of the intermediate bromide compound **9a** reverts back to the alcohol **9** due to its high reactivity. Further, upon standing in air, the bromide compound **9a** begins to decompose. Fortunately the primary alcohol, much like the phenolic alcohol, does not significantly affect the next step despite the basic conditions. Thus the 1,3-bis-methoxycarbonylpropylammonium chloride, BMPAC, displaces the bromide, forming **9b**.[20] It would be expected that the nitrogen then condenses directly to form the pyrollidinone ring in **10**; however, this reaction does not occur to a significant extent. Excess potassium carbonate does not necessarily increase the yield of amide, but



9 **9a** **9b** **10**

Scheme 5. Uncharacterizeable intermediates in tylophorinine synthesis

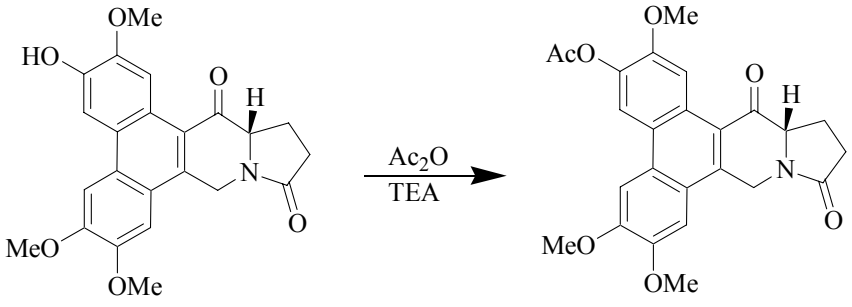
surely increases reversion to the alcohol **9**. Fortunately the phenolic hydroxy group does not interfere in this reaction to a noticeable extent. Further purification of the free amine **9b** is futile since it will slowly condense irreversibly on itself over time. Silica gel chromatography is ineffective, since it catalyzes this reaction, but interestingly the reaction does not proceed by simply stirring silica with a crude mixture of amine. Only upon column chromatography does this reaction occur. However, the crude mixture of **9b** may be converted to the amide **10** by heating in a solution of methanol and acetic acid. Amide **10** may then be separated from the reformed alcohol **9a** by silica gel chromatography. Thus, a convenient method to produce amide **10** has been attained.

1-(3-Hydroxy-2,6,7-trimeoxyphenanthren-9-ylmethyl)-5-oxo-pyrrolidine-2-carboxylic acid (**11**) is also easily formed[20] in short time and high yield. Because of this compound's insolubilty, all impurities can be washed away with cold water and chloroform. However, the insolubility advantage in this step quickly turns into a disadvantage for the remainder of the synthesis. The result of this problem is evident in obtaining the spectra for subsequent compounds. It is arguable that racemization may occur at this stage due to the strong basic conditions of the saponification step, i.e. converting **10** to **11**. However, an optical rotation was obtained for **11** that was comparable to that for **10**. This supports the contention that the asymmetric center is stable under basic reaction conditions.

The best illustration of solubility problems results with cyclization[20] of **11** to 3-hydroxy-2,6,7-trimethyl-12,12a-dihydro-9*H*,11*H*-9a-aza-cyclopenta[*b*]triphenylene-10,13-dione (**12**). Although **12** is relatively simple to produce, it must be noted that upon

formation, the compound almost immediately crashes out of solution. Column chromatography is best suited for purification of this compound, since the compound tends to decompose fairly rapidly. Here, the solubility issue also may raise questions as to whether the compound was actually produced. However, for the purposes of identification **12** was converted as shown in Scheme **6**, to the acetate **15**. The acetate **15** could be fully characterized by NMR spectroscopy and mass spectroscopy.

More importantly an optical rotation was obtained which further supports the stability of the asymmetric center, thus showing its relative invulnerability to both basic and acidic conditions. Also, the cyclization itself is a major accomplishment. Use of tin(IV) chloride provides the only effective methodology for cyclization of **11**, via the acid chloride, to the indolizidine ring system. Other attempts to cyclize the ring system, including traditional reagents, such as aluminum chloride and polyphosphoric acid, proved ineffective.



12 **15**

Scheme 6. Derivitization of **12** for spectral purposes

Another of Rapoport's finer accomplishments in this field was his mention of the use of L-Selectride for selective reduction of **12** to 3,13-dihydroxy-2,6,7-trimethoxy-11,12,12a,13-tetrahydro-9*H*-9a-aza-cyclopenta[*b*]triphenylen-10-one (**13**). Although he does not mention a standard procedure[20] for this reaction, it was discovered in the present research that the reaction must take place at –10 °C and for 9 hours for maximum stereoselectivity. Disregarding these two provisions causes the (R) hydroxy compound to be produced along with amide reduction. Of the two, the amide reduction poses the larger problem, since the two diastereomers are chromatographically separable only so long as the amide is present.

The end of the synthesis gives way to a simple lithium aluminum hydride reduction[29] of the amide to produce, 2,6,7-trimethoxy-9,10,11,12,12a,13-hexahydro-9a-aza-cyclopent[*b*]tripnylene-3,13-diol (**14**). The compound again proved spectroscopically difficult to analyze, utilizing TFA to aid in dissolving the compound.

b. Alternate route to synthesis of free hydroxy tylophorinine

It was also of interest to utilize vanadium oxytriflouride (VOF_3) as a reagent for the purpose of biaryl coupling in this synthesis. As mentioned, the free hydroxy group affects the reaction in such an adverse way the products are indistinguishable. However, with an appropriate protection strategy the problem was quickly overcome.

The first attempt to overcome the destructive nature of VOF_3 on reacting with free hydroxy groups was with the use of the methoxymethyl ether as a protecting group. Although the reaction was successful in the sense that a useable product **8**, was obtained, very low yield precludes any further consideration for using this protecting group. The

low yield is attributable to the loss of the ether, which frees the hydroxy group to activate the vanadium in some way to destroy the compound. This was shown after reaction workup, where the products were not characterizable.

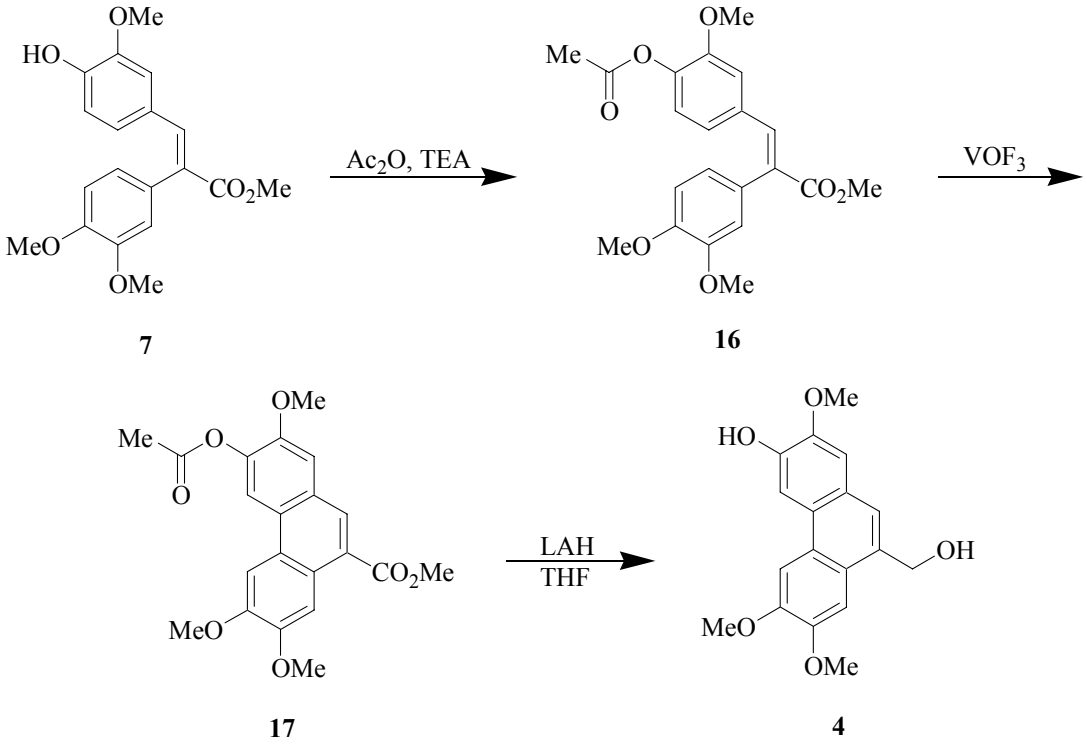
The more useful method represented in Scheme 7 shows protection of the phenolic hydroxy group in **7** with an acetyl group to 3-(4-acetoxy-3-methoxyphenyl)-2-(3,4-dimethoxyphenyl)acrylic acid methyl ester (**16**). This simple reaction is very high yielding. No purification of product is necessary to proceed to the next step.

The aromatic coupling to **17** from **16** proceeds in high yield and without loss of the acetyl group. The protecting group, however, does not pose a problem since we are able to proceed with simultaneous reduction of both esters to compound **9** in one step. Thus we return to a position in the primary sequence to finish the synthesis.

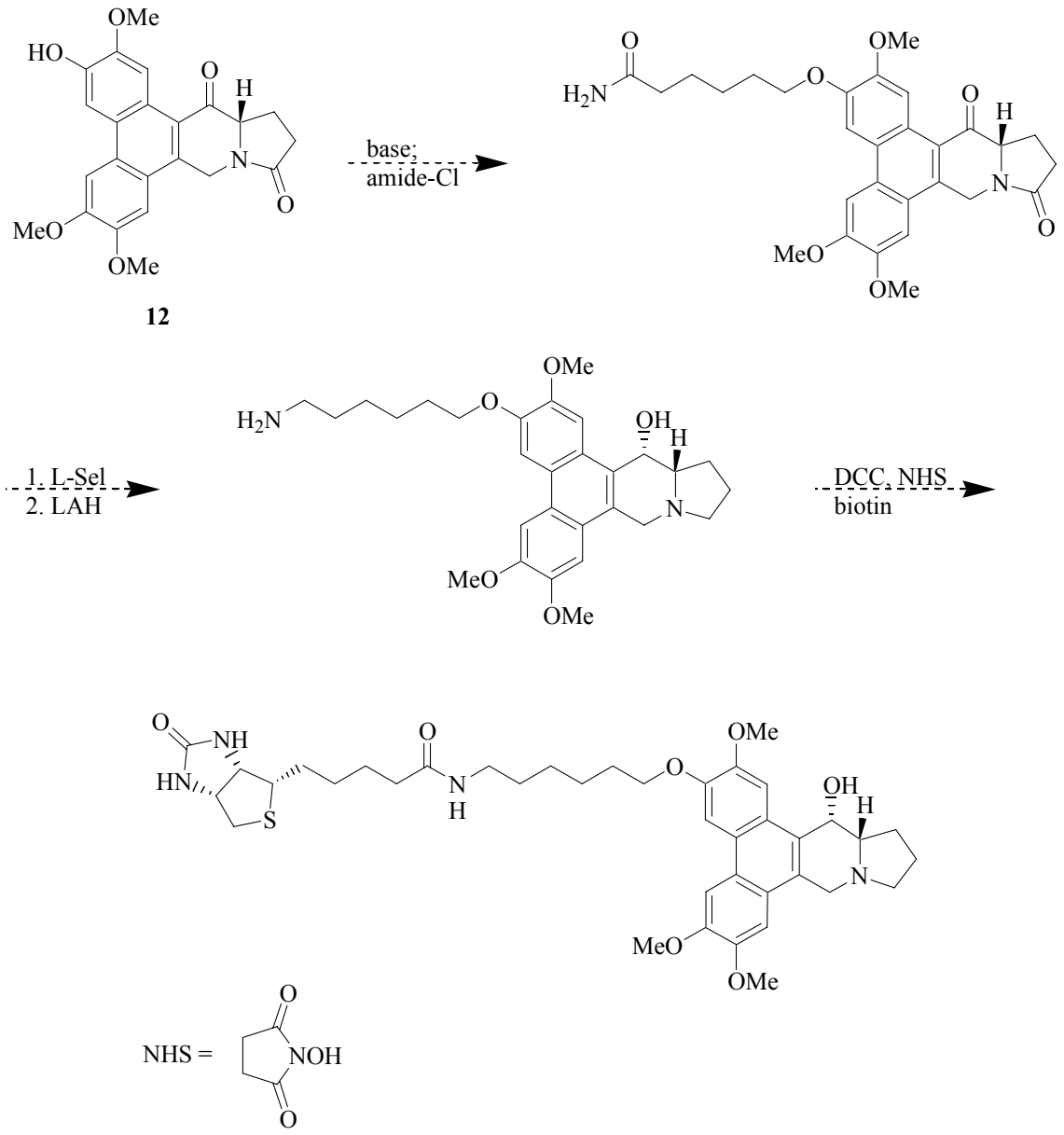
The advantage to using the vanadium reagent is that of savings in reaction time. A coupled product may be produced within one day, whereas the iron chloride requires two days, not accounting for purification. Despite the advantage of using VOF_3 in time, costs of the reagent may be prohibitive in large-scale production.

c. Attempts to synthesize the biotin-linked compound

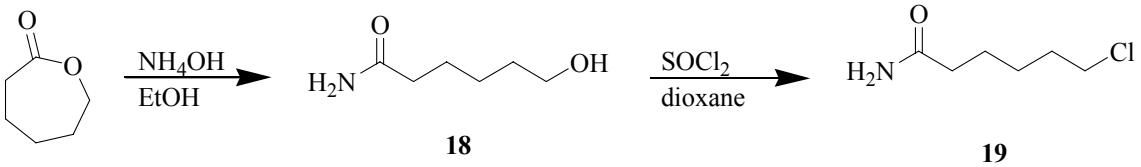
The simplest conceived route to obtain the desired compound is shown in Scheme 8. First the linker arm had to be prepared. This was done as shown in Scheme 9. The oldest and best known method for amide formation is through an ester to produce compound **18**, 6-hydroxyhexanoic acid amide. Since the nitrogen carbonyl bond is stronger than the oxygen carbonyl bond, the reaction is essentially reversible, although it



Scheme 7. Alternative route for free hydroxy tylophorinine synthesis



Scheme 8. Strategy towards biotinylation of tylophorinine



Scheme 9. Synthesis of the linker arm

does take time. 6-Chlorohexanoic acid amide (**19**), is then prepared for the alkylation, using the chloride as the leaving group. Attempts to synthesize the bromide, mesyl, or tosyl groups as leaving groups proved unsuccessful. What is even more distressing is that despite all attempts to alkylate **12**, no product was successfully isolated or satisfactorily confirmed. Many different bases, as well as solvent systems, or no solvent systems, were employed. Bases as strong as sodium hydride were employed. Other bases included NaOH, Cs_2CO_3, triethylamine, tetrabutylammonium hydroxide, diisopropylamine, K_2CO_3. Solvents included CH_2Cl_2, pyridine, acetone, DMF, and tetrahydrofuran. Hence it was decided that the best course of action would be to change the linker arm. This is attributable mainly to two reasons. The primary cause is believed to be steric effects caused by the adjacent methoxy group. Electronic effects due to the aromatic π-system as well as the adjacent oxygen atom also contributed. This is best illustrated with the acetylation to **15**, which took approximately 300 equivalents of both trimethylamine and acetic anhydride, and three hours at room temperature, for perhaps one of the simplest reactions. Even acetylation to **16** required large molar excesses of reagents and at least one hour at room temperature.

The greatest difficulty in designing the linker arm is that the experimentalist must consider the synthesis as a whole. The best types of linker arms would have to have the nitrogen already as the end group in some form. Two other potential linker arms are shown in Figures 4 and 5. Although the amide was not successfully produced, the nitrile could be purchased. However, even with the more reactive bromide leaving group, the alkylation proved unsuccessful, using the conditions previously discussed.

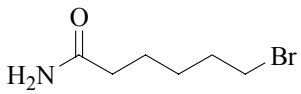


Figure 4. 6-bromohexanoic acid amide

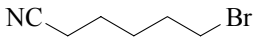


Figure 5. 6-bromohexanenitrile

d. Future work towards the biotin linkage

Due to the problems encountered in III.2.c, towards the synthesis of the biotin-linked compound, it is apparent that a new route for its synthesis must be developed. A possibility is to alkylate the phenanthrene ring system prior to cyclization of the indolizidine ring system. However, it is difficult to envision an efficient procedure, which will compensate for the various reaction condition, as well as maintain functional group stability, particularly if a nitrogen containing end group on the linker arm is present.

IV. Experimental

Preparation of (2,3,6,7-tetramethoxyphenanthren-9-ylmethyl)-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (2).[20,30] Compound **9** (1.632 g, 4.970 mmol) was dissolved in 100 mL of $CHCl_3$ and cooled to 0 ºC. A solution of PBr_3 (0.7 mL, 7.4 mmol) in 20 mL of $CHCl_3$ was added dropwise. The solution was then stirred at room temperature for 1.5 h, then poured over ice, and the two layers were separated. The organic phase was dried over Na_2SO_4, filtered, and rotary evaporated, and the product was placed under vacuum for 3 h. The solid was then redissolved in 140 mL of DMF. Glutamic acid dimethyl ester (1.5 g, 7.1 mmol) was added and allowed to stir for 15 min. K_2CO_3 (1 g, 7.2 mmol) was added, and the mixture was allowed to stir at room temperature overnight. The solution was then rotary evaporated, and the product was partitioned between $CHCl_3$ and H_2O. The organic layer was dried over Na_2SO_4, filtered, and rotary evaporated. The crude product was dissolved in 25 mL of MeOH and 10 mL of HOAc and stirred for 3 h at 45 ºC. The solution was rotary evaporated, and the crude product was purified by column chromatography (2:1 hexane:EtOAc) to give 1.145 g of **2** (50.80% yield). ^{1}H NMR ($CDCl_3$): δ 2.071 (2 H, m), 2.390 (1 H, m), 2.591 (1 H, m), 3.564 (3 H, s), 3.840 (1 H, dd, J = 3 Hz, J = 9 Hz), 4.019 (6 H, s), 4.103 (3 H, s), 4.108 (3 H, s), 4.389 (1 H, d, J = 14.7 Hz), 5.489 (1 H, d, J = 14.7 Hz), 7.157 (1 H, s), 7.389 (1 H, s), 7.598 (1 H, s), 7.751 (1 H, s), 7.787 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 22.745, 29.802, 44.777, 52.236, 55.943, 56.019, 56.106, 56.341, 58.538, 102.746, 103.114, 105.307, 108.229, 124.835, 124.892, 125.571, 126.918, 127.100, 148.939, 149.098, 149.201, 149.626, 172.276, 172.276.

Preparation of (2,3,6,7-trimethoxyphenanthren-9-ylmethyl)-5-oxo-pyrrolidine-2-carboxylic acid (3).[20] Compound **2** (1.145 g, 2.3345 mmol) was stirred in a solution of 30 mL of dioxane, 24 mL of MeOH, and 15 mL of 2 N KOH for 1.5 h. The solution was cooled to 0 ºC and 85% H_3PO_4 was added until pH 4. The mixture was rotary evaporated, and the resulting solid was washed with cold H_2O to give 1.003 g of **3** (90.39% yield). ^{1}H NMR (DMSO-d_6): 1.888 (2 H, m), 2.125 (2 H, m), 2.376 (2 H, m), 3.671 (1 H, d, J = 6.9 Hz), 3.846 (3 H, s), 3.885 (3 H, s), 4.006 (6 H, s), 4.186 (1 H, d, J = 14.7 Hz), 5.401 (1 H, d, J = 14.7), 7.356 (1 H, s), 7.442 (1 H, s), 7.471 (1 H, s), 7.971 (1 H, s), 8.013 (1 H, s); ^{13}C NMR (DMSO-d_6): δ 22.370, 29.256, 43.666, 55.431, 55.458, 55.905, 55.966, 57.977, 103.710, 104.298, 104.833, 108.487, 124.175, 124.274, 124.661, 125.272, 125.776, 126.975, 148.609, 148.707, 148.969, 149.383, 173.224, 174.260.

Preparation of 2,3,6,7-tetramethyl-12,12a-dihydro-9*H*,11*H*-9a-aza-cyclopenta[*b*]triphenylene-10,13-dione (4).[20] To a solution of **3** (1.003 g, 2.282 mmol) in 80 mL of CH_2Cl_2 was added oxalyl chloride (0.4 mL, 4.6 mmol) and 0.05 mL of DMF. The mixture was stirred for 1.5 h then brought to 35 ºC. $SnCl_4$ (0.5 mL, 4.27 mmol) was added, and the mixture was stirred for an additional 4 h. The solution was cooled to room temperature, and 70 mL of cold 2 N HCl was added. The phases were separated, and the organic phase was dried over Na_2SO_4 and filtered. The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography (99:1 chloroform:MeOH) to give 818.4 mg of **4** (85.08% yield). ^{1}H NMR ($CDCl_3$): δ 2.570 (3 H, m), 2.905 (1 H, d, J = 22.2 Hz), 4.067 (3 H, s), 4.075 (3 H, s), 4.111 (3 H, s), 4.148 (3 H, s), 4.420 (1 H, m), 4.702 (1 H, d, J = 17.7 Hz), 5.731 (1 H, d, J = 17.7), 7.288 (1 H, s),

7.762 (1 H, s), 7.784 (1 H, s), 9.082 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 20.776, 30.071, 40.850, 55.856, 55.909, 56.045, 56.201, 61.202, 102.451, 102.974, 104.226, 107.637, 121.720, 122.107, 123.371, 124.668, 128.205, 137.542, 149.114, 149.368, 149.925, 151.986, 174.018, 195.788.

Preparation of 13-Hydroxy-2,3,6,7-tetramethoxy-11,12,12a,13-tetrahydro-9*H*-9a-aza-cyclopenta[*b*]triphenylen-10-one (5).[20] To a solution containing **4** (818.4 mg, 1.942 mmol) in 20 mL of THF at –10 ºC was added 1 M L-Selectride (2.2 mL, 2.2 mmol). The solution was stirred for an additional 5 h, then 0.5 mL of 2 N HCl was added. The solution was partitioned between $CHCl_3$ and H_2O. The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed by rotary evaporation. The crude product was purified by column chromatography (98:2 chloroform:MeOH) to give 673.3 mg of **5** (81.88% yield). ^{1}H NMR ($CDCl_3$): δ 2.549 (4 H, m), 3.747 (3 H, s), 3.894 (1 H, d, J = 8.4 Hz), 4.072 (3 H, s), 4.080 (3 H, s), 4.100 (3 H, s), 4.342 (1 H, d, J = 17.4 Hz), 5.091 (1 H, d, J = 17.4), 5.117 (1 H, d), 6.742 (1 H, s), 7.591 (1 H, s), 7.663 (1 H, s), 7.711 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 19.239, 30.842, 40.934, 55.894, 56.053, 58.409, 65.694, 102.765, 102.910, 103.035, 103.171, 104.283, 122.639, 123.849, 124.240, 124.414, 124.695, 126.823, 148.795, 149.004, 149.148, 149.322, 175.376.

Preparation of 2,3,6,7-Tetramethoxy-9,10,11,12,12a,13-hexahydro-9a-aza-cyclopent[*b*]tripnylene-13-ol (1).[20] To a mixture of LAH (350 mg, 9.22 mmol) in 100 mL of THF at 0 ºC was added dropwise a solution of **5** (615.3 mg, 1.453 mmol) in 50 mL of THF. The mixture was stirred for 6 h at room temperature then brought back to 0 ºC, at which point 25 mL of EtOAc was added dropwise, followed by 50 mL of H_2O. The

solution was filtered, and the solvent was removed by rotary evaporation. The product was purified by column chromatography (98:2 chloroform:MeOH) to give 399 mg **1** (67.06 % yield); ^{1}H NMR ($CDCl_3$): δ 1.801 (2 H, m), 2.095 (3 H, m), 2.362 (1 H, m), 2.709 (1 H, d, J = 14.4 Hz), 2.950 (1 H, d, J = 13.8), 3.251 (1 H, s), 3.691 (3 H, s), 4.052 (3 H, s), 4.075 (3 H, s), 4.110 (3 H, s), 4.711 (1 H, s), 5.769 (1 H, s), 7.257 (1 H, s), 7.528 (1 H, s), 7.873 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 21.565, 23.800, 29.684, 53.006, 55.541, 55.571, 55.844, 56.148, 64.593, 65.466, 101.840, 102.348, 102.466, 105.277, 122.350, 123.648, 125.841, 127.400, 147.520, 148.188, 148.324, 148.522; ^{1}H NMR (DMSO-d_6 + TFA): δ 2.132 (4 H, m), 3.415 (1 H, m), 3.777 (2 H, m), 3.955 (3 H, s), 3.964 (3 H, s), 4.041 (6 H, s), 4.599 (1 H, dd, J = 8.7 Hz, J = 15.6), 5.146 (1 H, d, J = 12.9), 5.522 (1 H, d, J = 1.5 Hz), 7.233 (1 H, s), 7.629 (1 H, s), 8.043 (1 H, s), 8.060(1 H, s); ^{13}C NMR (DMSO-d_6 + TFA): δ 20.572, 23.079, 51.155, 53.921, 55.594, 55.742, 55.962, 60.731, 65.872, 103.919, 104.074, 104.279, 105.163, 121.178, 121.831, 123.959, 124.266, 124.391, 127.279, 148.924, 149.007, 149.269, 149.603.

Synthesis of 3-(4-Acetoxy-3-methoxyphenyl)-2-(3,4-dimethoxyphenyl)acrylic acid (6). Vanillin (30.48 g, 200.3 mmol), homoveratric acid (39.48 g, 201.4 mmol), Et_3N (70 mL, 502 mmol), and Ac_2O (110 mL, 1163 mmol) were stirred at 100 ºC. After 24 h the mixture was cooled to room temperature, followed by slow addition of 100 mL of H_2O. Then a solution of 150 g of K_2CO_3 in 500 mL of H_2O was added, and the mixture was refluxed until all the solid dissolved. The mixture was then cooled to room temperature, and washed with 2 × 100 mL of Et_2O. The aq layer was then acidified with concd HCl to pH 1. The resulting precipitate was recrystallized from MeOH to give 47.96 g of **6**

(64.44% yield). mp 170.9–176.2; ^{1}H NMR ($CDCl_3$): δ 2.259 (3 H, s), 3.440 (3 H, s), 3.798 (3 H,s), 3.877 (3 H, s), 6.658 (1 H, d, J = 1.8 Hz), 6.639 (1 H, d, J = 1.8 Hz), 6.755 (1 H, d, J = 2.1 Hz), 6.790 (1 H, dd, J = 1.8 Hz, J = 4.5 Hz), 6.817 (1 H, dd, J = 2.1 Hz, J = 4.2 Hz), 6.875 (1 H, d, J = 4.2 Hz), 6.902 (1 H, d, J = 4.2), 7.846 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 20.910, 55.603, 56.161, 56.179, 111.668, 112.817, 114,141, 122.408, 122.917, 124.814, 127.739, 131.347, 133.305, 140.878, 141.819, 149.077, 149.502, 150.754, 169.053, 173.382 Anal. Calcd for $C_{20}H_{18}O_6$: C, 64.51; H, 5.41. Found: C, 64.63; H, 5.50.

Synthesis of 2-(3,4-Dimethoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)acrylic acid methyl ester (7). Compound **6** (12.03 g, 32.31 mmol) was added to 600 mL of dry MeOH. Concd H_2SO_4 (12 mL) was added, and the solution was stirred at 65 ºC for 8 h. The MeOH was removed by rotary evaporation, and the solid was redissolved in $CHCl_3$ and washed with satd aq $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and rotary evaporated. The solid was purified by column chromatography (2:1 hexane:EtOAc). Yield 10.63 g (95.57%). mp 121.7–123.5; ^{1}H NMR ($CDCl_3$): δ 3.484 (3 H, s), 3.786 (3 H, s), 3.811 (3 H, s), 3.894 (3 H, s), 5.809 (1 H, s), 6.464 (1 H, s), 6.762 (3 H, m), 6.867 (1 H, dd, J = 1.8 Hz, J = 8.1 Hz), 6.914 (1 H, d, J = 8.1 Hz), 7.748 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 52.289, 55.260, 55.844, 111.370, 111.958, 112.763, 114.068, 122.123, 125.970, 126.884, 128.732, 129.176, 140.562, 145.794, 146.814, 148.453, 149.170, 168.607 Anal. Calcd for $C_{19}H_{18}O_5$: C, 66.27; H, 5.85. Found: C, 66.11; H, 5.94.

Synthesis of 3-Hydroxy-2,6,7-trimethylphenanthrene-9-carboxylic acid methyl ester (8). Compound **7** (3.00 g, 8.717 mmol) was dissolved in 400 mL of CH_2Cl_2. $FeCl_3 \cdot 6H_2O$

(50 g, 185 mmol) was added to 100 mL of CH_2Cl_2, and the mixture was allowed to stir for 48 h. The solution was filtered, and the solvent was removed by rotary evaporation. The crude product was purified by column chromatography (1.5:1 hexane:EtOAc) to give 1.02 g of **8** (34.39% yield). mp 191.6–193.1 °C; ^{1}H NMR ($CDCl_3$): δ 4.011 (3 H, s), 4.073 (3 H, s), 4.110 (3 H, s), 4.133 (3 H, s), 5.927 (1 H, s), 7.364 (1 H, s), 7.700 (1 H, s), 7.739 (1 H, s), 8.341 (1 H, s), 8.615 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 52.336, 56.081, 56.142, 56.288, 101.852, 102.755, 107.068, 112.715, 122.617, 124.176, 125.235, 125.463, 127.018, 130.864, 145.552, 149.160, 149.251, 149.327, 168.552. Anal. Calcd for $C_{19}H_{16}O_5$: C, 66.66; H, 5.30. Found: C, 66.39; H, 5.40.

Synthesis of 9-Hydroxymethyl-2,6,7-trimethoxyphenanthren-3-ol (9). Method A. To a mixture of LAH (3.8226 g, 100.73 mmol) in 300 mL of THF at 0 ºC was added dropwise a solution of **8** (5.7829g, 16.892 mmol) in 30 mL of THF. The solution was stirred at room temperature for an additional 4 h, then brought back to 0 ºC, at which point 50 mL of EtOAc was added dropwise, followed by 70 mL of 2 N HCl. The solution was filtered, and the solvent was removed by rotary evaporation. The product was purified by column chromatography (1:2 hexane:EtOAc) to give 3.17 g of **9** (90.44% yield). mp 189.4–192.1 °C ^{1}H NMR ($CDCl_3$): δ 4.026 (3 H, s), 4.035 (3 H, s), 4.080 (3 H, s), 5.098 (2 H, s), 7.175 (1 H, s), 7.504 (1 H, s), 7.546 (1 H, s), 7.821 (1 H, s), 7.946 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 55.951, 55.932, 55.951, 64.779, 103.437, 104.587, 106.024, 107.679, 124.092, 124.498, 125.040, 125.374, 125.469, 131.741, 145.794, 146.492, 148.795, 148.973 Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.73; H, 5.89. Method B. A solution of **17** (2.0013 g, 5.207 mmol) in 100 mL of THF was

added dropwise to a mixture of $LiAlH_4$ (2 g, 53 mmol) and 30 mL of THF at 0 ºC. The mixture was then warmed to room temperature and stirred for 4 h. The mixture was cooled to 0 ºC, and 60 mL of EtOAc, followed by 40 mL of 2 N HCl were added dropwise. The mixture was filtered and the mother liquor was rotary evaporated. The crude product was purified by column chromatography (1:2 hexane:EtOAc) to give 1.5474 g of **9** (94.55% yield). The product was identical with that produced in Method A by NMR spectroscopy.

Synthesis of 1-(3-Hydroxy-2,6,7-trimethoxyphenanthren-9-ylmethyl)-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (10). Compound **9** (1.5067 g, 4.7966 mmol) was dissolved in 100 mL of $CHCl_3$ and cooled to 0 ºC. A solution of PBr_3 (0.7 mL, 7.4 mmol) in 20 mL of $CHCl_3$ was added dropwise. The solution was then stirred at room temperature for 1.5 h, then poured over ice, and the two layers were separated. The organic phase was dried over Na_2SO_4, filtered, and rotary evaporated, and the product was placed under vacuum for 3 h. The solid was then redissolved in 140 mL of DMF. Glutamic acid dimethyl ester (1.5 g, 7.1 mmol) was added and allowed to stir for 15 min. K_2CO_3 (1 g, 7.2 mmol) was added, and the mixture was allowed to stir at room temperature overnight. The solution was then rotary evaporated, and the product was partitioned between $CHCl_3$ and H_2O. The organic layer was dried over Na_2SO_4, filtered, and rotary evaporated. The crude product was dissolved in 25 mL of MeOH and 10 mL of HOAc and stirred for 3 h at 45 ºC. The solution was rotary evaporated, and the crude product was purified by column chromatography (1:1 hexane:EtOAc) to give 1.2093 g of **10** (57.41% yield). mp 200 °C dec; $[\alpha]^{21.5}_D$ 83.56° ($CHCl_3$) ^{1}H NMR ($CDCl_3$): δ 2.042 (2

H, m), 2.376 (1 H, m), 2.581 (1 H, m), 3.551 (3 H, s), 3.833 (1 H, dd, J = 3.3 Hz, J = 9.3 Hz), 4.005 (3 H, s), 4.027 (3 H, s), 4.064 (3 H, s), 4.375 (1 H, d, J = 14.4 Hz), 5.470 (1 H, d, J = 14.4 Hz), 7.137 (1 H, s), 7.359 (1 H, s), 7.565 (1 H, s), 7.793 (1 H, s), 7.936 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 22.677, 29.764, 44.739, 52.183, 55.822, 55.943, 56.273, 58.512, 103.270, 105.034, 105.971, 107.497, 124.646, 124.832, 125.162, 125.545, 126.694, 126.903, 145.968, 146.499, 149.049, 172.269, 174.617. EIMS: Calcd for $C_{24}H_{25}NO_7$, *m/z* 439.1631; found *m/z* 439.1622.

Synthesis of 1-(3-Hydroxy-2,6,7-trimethoxyphenanthren-9-ylmethyl)-5-oxo-pyrrolidine-2-carboxylic acid (11). Compound **10** (1.0259 g, 2.3345 mmol) was stirred in a solution of 30 mL of dioxane, 24 mL of MeOH, and 15 mL of 2 N KOH for 1.5 h. The solution was cooled to 0 ºC and 85% H_3PO_4 was added until pH 4. The mixture was rotary evaporated, and the resulting solid was washed with cold H_2O to give 0.9784 g **11** (98.52% yield). mp 320 °C dec; $[\alpha]^{21.5}_D$ 79.77° (DMSO) ^{1}H NMR (DMSO-d_6): 2.370 (m), 3.652 (d, J = 6.9 Hz), 3.829 (s), 3.905 (s), 3.961 (s), 4.150 (d, J = 13.2 Hz), 5.391 (d, J = 14.4), 7.323 (s), 7.401 (s), 7.441 (s), 7.838 (s), 7.941 (s); ^{13}C NMR (DMSO-d_6): 23.005, 29.944, 31.371, 44.350, 56.108, 56.218, 58.570, 104.436, 105.514, 107.638, 109.217, 124.692, 124.988, 125.250, 125.421, 126.718, 147.851, 148.754, 149.156, 149.456, 173.939, 174.895. Anal. Calcd for $C_{23}H_{23}NO_7 \cdot 0.5\ H_2O$: C, 63.59; H, 5.57; N, 3.22. Found: C, 63.43; H, 5.82; N, 2.92.

Synthesis of 3-Hydroxy-2,6,7-trimethyl-12,12a-dihydro-9*H*,11*H*-9a-aza-cyclopenta[*b*]triphenylene-10,13-dione (12). To a solution of **11** (1.103 g, 2.610 mmol) in 80 mL of CH_2Cl_2 was added oxalyl chloride (0.8 mL, 9.2 mmol) and 0.05 mL of DMF.

The mixture was stirred for 1.5 h then brought to 35 ºC. $SnCl_4$ (1.2 mL, 10.25 mmol) was added, and the mixture was stirred for an additional 4 h. The solution was cooled to room temperature, and 70 mL of cold 2 N HCl was added. The phases were separated, and the organic phase was dried over Na_2SO_4 and filtered. The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography (98:2 chloroform:MeOH) to give 0.8273 g of **12** (78.32% yield). mp 240 °C; EIMS: Calcd for $C_{23}H_{21}NO_6$ *m/z* 407.1369; found *m/z* 407.1362.

Synthesis of 3,13-Dihydroxy-2,6,7-trimethoxy-11,12,12a,13-tetrahydro-9*H*-9a-aza-cyclopenta[*b*]triphenylen-10-one (13). To a solution containing **12** (328.4 mg, 0.8060 mmol) in 20 mL of THF at –10 ºC was added 1 M L-Selectride (1.2 mL, 1.2 mmol). The solution was stirred for an additional 5 h, then 0.5 mL of 2 N HCl was added. The solution was partitioned between $CHCl_3$ and H_2O. The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed by rotary evaporation. The crude product was purified by column chromatography (98:4 chloroform:MeOH) to give 241.8 mg **13** (73.68% yield). mp 160 °C dec; $[\alpha]^{21.5}_D$ 71.39° ($CHCl_3$) ^{1}H NMR ($CDCl_3$): δ 2.300 (1 H, m), 2.560 (3 H, m), 3.937 (3 H, s), 4.062 (3 H, s), 4.078 (3 H, s), 4.447 (1 H, d, J = 8.4 Hz), 5.130 (1 H, d, J = 1.2), 5.280 (1 H, d, J = 8.4 Hz), 7.003 (1 H, s), 7.544 (1 H, s), 7.713 (1 H, s), 7.914 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 19.342, 29.681, 40.896, 55.871, 56.068, 56.125, 58.269, 65.842, 102.971, 103.300, 103.433, 106.484, 122.601, 123.864, 124.202, 124.608, 125.033, 126.615, 145.517, 146.924, 149.068, 149.504 EIMS Calcd for $C_{23}H_{23}NO_6$ *m/z* 409.1525; found *m/z* 409.1520.

Synthesis of 2,6,7-Trimethoxy-9,10,11,12,12a,13-hexahydro-9a-aza-cyclopent[*b*]tripnylene-3,13-diol (14). To a mixture of LAH (30 mg, 0.79 mmol) in 15 mL of THF at 0 ºC was added dropwise a solution of **13** (60 mg, 0.15 mmol) in 10 mL of THF. The mixture was stirred for 6 h at room temperature then brought back to 0 ºC, at which point 5 mL of EtOAc was added dropwise, followed by 7 mL of H_2O. The solution was filtered, and the solvent was removed by rotary evaporation. The product was purified by column chromatography (98:2 chloroform:MeOH) to give 22.6 mg of **14** (78.00% yield). mp 145 °C; $[\alpha]^{21.5}_D$ 82.39° ($CHCl_3$) ^{1}H NMR ($CDCl_3$ + TFA): δ 2.05 (1 H, m), 2.237 (3 H, m), 3.405 (1 H, m), 3.717 (1 H, m), 3.935 (3 H, s), 3.977 (3 H, s), 3.992 (3 H, s), 4.555 (1 H, dd, J = 3.3 Hz, J = 16.8 Hz), 7.192 (1 H, s), 7.600(1 H, s), 7.886(1 H, s), 8.045(1 H, s) ^{13}C ($CDCl_3$ + TFA) δ 20.522, 23.038, 51.038, 53.853, 55.575, 55.659, 55.727, 60.697, 65.838, 103.718, 103.862, 105.224, 107.428, 120.233, 121.614, 123.177, 124.065, 124.646, 127.324, 147.091, 148.248, 148.798, 149.364, 158.094, 158.583. EIMS: Calcd for $C_{23}H_{25}NO_5$ *m/z* 395.1733; found *m/z* 395.1728.

Synthesis of 3-acetoxyl-2,6,7-trimethoxy-10,13-dioxo-9,10,11,12,12a,13-hexahydro-9a-aza-cyclopenta[*b*]triphenylene (15). Compound **12** (49.6 mg, 0.1217 mmol), Et_3N (2 mL, 27.22 mmol), Ac_2O (3.5 mL, 31.74 mmol) stirred at room temperature for 3 h. The crude mixture was partitioned between $CHCl_3$ and H_2O, and the organic layer was dried with Na_2SO_4. The resulting solution was removed by rotary evaporation and separated by column chromatography (98:2 $CHCl_3$:MeOH) to give 50.3 mg of **15** (91.93% yield). $[\alpha]^{21.5}_D$ 138.62° ($CHCl_3$) ^{1}H NMR ($CDCl_3$): δ 2.406 (3 H, s), 2.559 (3 H, m), 3.205 (1 H, m), 4.010 (3 H, s), 4.048 (3 H, s), 4.116 (3 H, s), 4.375 (1 H, m), 4.644 (1

H, d, J = 18 Hz), 5.689 (1 H, d, J = 18 Hz), 7.229 (1 H, s), 7.718 (1 H, s), 8.092 (1 H, s), 9.162 (1 H, s) ^{13}C NMR ($CDCl_3$): δ 20.734, 20.768, 30.030, 40.877, 55.947, 56.076, 56.186, 61.076, 103.152, 104.135, 108.904, 115.673, 121.425, 121.872, 124.198, 127.362, 128.356, 139.701, 140.031, 149.493, 151.037, 152.209, 169.211, 174.029, 195.435 EIMS: Calcd for $C_{25}H_{23}NO_7$ *m/z* 449.1475; found *m/z* 449.1480

Synthesis of 3-(4-Acetoxy-3-methoxyphenyl)-2-(3,4-dimethoxyphenyl)acrylic acid methyl ester (16). Compound **3** (4.9003 g, 14.314 mmol) was added to Et_3N (25 mL, 179 mmol) and Ac_2O (50 mL, 529 mmol), and the mixture was stirred at room temperature for 1 h. The solution was rotary evaporated. The crude product was purified by column chromatography (2:1 hexane:EtOAc) to give 5.2195 g of **16** (94.43% yield). mp 110.5–114.8 °C; ^{1}H NMR ($CDCl_3$): 2.252 (3 H, s), 3.432 (3 H, s), 3.784 (3 H, s), 3.788 (3 H, s), 3.871 (3 H, s), 6.598 (1 H, d, J = 1.8 Hz), 6.724 (1 H, d, J = 2.1 Hz), 6.753 (1 H, dd, J = 1.8 Hz, J = 6.3 Hz), 6.780 (1 H, dd, J = 2.1 Hz, J = 6.0 Hz), 6.856 (1 H, d, J = 6.0 Hz), 6.883 (1 H, d, J = 6.3 Hz), 7.741 (1 H, s); ^{13}C NMR ($CDCl_3$): 20.617, 52.471, 55.306, 55.871, 55.897, 111.382, 112.607, 113.726, 122.081, 122.540, 124.160, 128.076, 131.919, 133.364, 139.572, 140.224, 148.662, 149.182, 150.407, 168.334, 168.786. Anal Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.34; H, 5.84.

Synthesis of 3-Acetoxy-2,6,7-trimethoxyphenanthrene-9-carboxylic acid methyl ester (17). Compound **16** (3.9 g, 10 mmol) was dissolved in 36 mL of dry CH_2Cl_2 and cooled to –10 ºC. A solution of VOF_3 (4 g, 32 mmol), 70 mL of CH_2Cl_2, 35 mL of EtOAc, 2 mL of TFA, and 5 drops of TFAA were added dropwise, and the solution was allowed to stir at –10 ºC for 4 h. The solution was poured over ice, and the product was

partitioned with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, filtered, and rotary evaporated. The crude product was purified by column chromatography (1:1 hexane:EtOAc) to give 3.5612 g of **17** (91.79% yield). 232.7–234.2 °C; ^{1}H NMR ($CDCl_3$): 2.407 (3 H, s), 3.955 (3 H, s), 4.002 (3 H, s), 4.050 (3 H, s), 4.070 (3 H, s), 7.301 (1 H, s), 7.705 (1 H, s), 8.089 (1 H, s), 8.344 (1 H, s), 8.524 (1 H, s); ^{13}C NMR ($CDCl_3$): 20.753, 52.164, 55.791, 55.822, 55.947, 102.663, 106.639, 110.187, 116.101, 123.572, 124.410, 125.465, 126.334, 128.550, 129.874, 141.852, 149.224, 149.254, 150.013, 168.053, 169.222. Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.84; H, 5.32.

Synthesis of 6-hydroxyhexanoic acid amide (18). To a solution of EtOH (500 mL) was added caprolactone (50 mL, 451 mmol). While stirring, NH_4OH (100 mL) was added in excess, and the solution was allowed to stir at room temperature for 2 days. The solution was then rotory evaporated to a gel and recrystallized from EtOH to give 15 g of **18** (25% yield). ^{1}H NMR ($CDCl_3$): 1.363 (2 H, m), 1.628 (4 H, m), 2.285 (2 H, t, J = 7.5 Hz), 4.034 (2 H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): 24.547, 25.496, 28.307, 34.097, 64.153, 173.600 Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 54.63; H, 10.01; N, 10.28.

Synthesis of 6-chlorohexanoic acid amide (19). To a soluton of **18** (2 g, 15 mmol) 60 mL of dioxane was added $SOCl_2$ (8 mL, 110 mmol). The solution is stirred for 1 h, then the solvent was removed by rotary evaporation. The crude product was purified by column chromatography (98:2 $CHCl_3$:MeOH) to give 1.8790 g of **19** (82% yield). ^{1}H NMR ($CDCl_3$): 1.461 (2 H, m), 1.643 (2 H, dt, J = 7.5, J = 7.8), 1.769 (2 H, dt, J = 6.6, J

= 7.2), 2.221 (2 H, dt, J = 6.6, J = 7.0), 2.221 (2 H, t, J = 7.5), 3.512 (2 H, t, J = 6.6); ^{13}C NMR ($CDCl_3$): 24.612, 26.384, 32.204, 35.512, 44.796, 175.452. Anal. Calcd for $C_6H_{12}ClNO$: C, 48.17; H, 8.08; N, 9.36; Cl, 23.70. Found: C, 48.27; H, 7.99; N, 9.24; Cl, 23.62.

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Vita

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